Claim Rejections - 35 USC § 112, first paragraph

Claims 13-22 are rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the disclosure of the specification such that the skilled artisan can make and use the invention. Applicant respectfully traverses.

The Examiner's rejection is based on:

a) whether any genetic ocular disease or a non-genetically based ocular disease associated with a lysosomal storage disease could be treated i.e. providing specific vector constructs comprising specific transgenes and appropriate dosages for a particular ocular disease

b) whether a therapeutically effective amount of protein can be achieved

c) whether effective delivery can be achieved in postmitotic cells

d) whether dominant mutational effects can be overcome.

The test of enablement is whether the disclosure provides sufficient information regarding the subject matter to practice the claimed invention without undue experimentation. Applicant submits that the present specification provides such information.

The present claims are directed to methods of treating ocular disease and to an *in situ* ocular cell containing exogeneous nucleic acid. The present disclosure describes methods that for the first time generated genetically engineered ocular cells *in situ* (*see* claims of parent, U.S. Patent No. 5,827,702). The methods provided herein open the door for ocular gene therapy, allowing for treatment of virtually any ocular disease for which a protein associated with the disease or useful for treating the disease is identified.

In support of this position, Applicant submits several references to show that the specification is fully enabling. While these references were published

after the priority date of the present application, the applicants are not using subsequent work to supplement the disclosure of the application; rather, the subsequent work is presented to show that the utility asserted and shown in the application is supported by further research, and that the specification fully enables therapeutic use of ocular gene therapy. See *In re Wilson*, 135 USPQ 442, 444 (CCPA 1962); *Ex parte Obukowicz*, 27 USPQ 2d 1063 (BPAI 1993); *Gould v. Quigg*, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> "it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative."

Previously, Applicant submitted a paper by Bennett *et al.* (*Nat. Med. 2(6)*:649-54 (1996), submitted with the response filed October 9, 1999 in the parent case, cited in the present IDS as reference 24 on form 1449 and enclosed herein as Exhibit A) (Bennett I) which shows the rescue of retinal cells in a model of inherited retinal degeneration (rd mouse) using essentially the methods of the present claims. This reference used the gene for cGMP phosphodiesterase beta subunit (β-PDE, cited in the present specification, for instance, at page 3, lines 16-17), and the same viral vector and promoter sequence used in the present examples. Thus, effective treatment of an ocular disease was achieved using the claimed methods, virtually exactly as presently exemplified.

Another example of the utilization of the presently claimed ocular gene therapy methods is found in Akimoto *et al.*, (*Invest. Opthamol. Vis. Sci. 40(2)*:273-79 (1999), a copy of which is enclosed as Exhibit B), in which retinal cell rescue was achieved in the Royal College of Surgeons (RCS) rat model of inherited retinal degeneration. Akimoto *et al.* shows that an adenovirus expressing basic fibroblast growth factor (bFGF, discussed at page 15, lines 28-

31 of the specification) under the control of a hybrid β-actin-CMV promoter (discussed at page 14, lines 6-8 of the specification) and introduced into the eye as presently described can be used as an effective treatment for this ocular disease.

Still further evidence of the enablement of the present invention is found in Li *et al.*, (*PNAS 92(17)*:7700-4 (1995), a copy of which is enclosed as Exhibit C). Li *et al.* shows that vector injections into the eye of a mouse deficient in β-glucuronidase can correct the pathology in this model of a lysosomal storage disease (*see*, for example, page 10, lines 24). The adenovirus vector expressing β-glucuronidase (discussed at page 3, line 28 to page 4, line 2 of the specification) under the control of a Rous sarcoma virus (RSV) promoter (well known in the art) provides evidence that effective promoters for the present treatments are not limited to those comprising CMV.

Effective treatment of ocular disease using the present invention has also been shown using vectors other than adenovirus. For instance, Jomary *et al.*, (*Gene Ther. 4(7)*:683-90 (1997), a copy of which is enclosed as Exhibit D), shows photoreceptor rescue in rd mice using an adenoassociateded vector (discussed, for example, at page 12, line 31 to page 13, line 1) expressing β-PDE. Similarly, Takahashi *et al.*, (*J. Virol. 73(9)*:7812-16 (1999), a copy of which is enclosed as Exhibit E), shows that injection of the human immunodeficiency virus (HIV) type 1 expressing β-PDE under the control of a CMV promoter is an effective means of treating retinal degeneration in rd mice.

Several other examples of effective treatment of ocular disease using the present methods are available. For instance, Bennett *et al.*, (*Gene Therapy 5*:1156-64 (1998), a copy of which is enclosed as Exhibit F) (Bennett II), shows extended survival of photoreceptors in rd mice after injecting an adenovirus expressing bcl-2 (known to control cellular apoptosis) under the control of a CMV promoter. The adenovirus and CMV promoter have also been used to

treat rd mouse retinal degeneration with nucleic acid encoding ciliary neurotrophic factor (CNTF: Cayouette *et al.*, *Human Gene Therapy 8*:423-30 (1997), a copy of which is enclosed as Exhibit G) and this photoreceptor rescue has been shown to have lasting effects on retinal function (*see* Cayouette *et al.*, *J. Neurosci. 10(22)*:9282-93 (1998), a copy of which is enclosed as Exhibit H). In addition, Ma *et al.*, (*Blood 90(7)*:2738-46 (1997), a copy of which is enclosed as Exhibit I), shows a reduction in metastasis of uveal melanoma upon ocular injection of an adenovirus expressing plasminogen activator inhibitor (PAI) under the control of a CMV promoter.

The list of references above show the efficacy of the present methods. Each of the references cited above follow the procedures described in the present specification. They show that incorporation of an exogenous nucleic acid into an *in situ* ocular cell, when the nucleic acid encodes a protein associated with (for example, β-PDE or β-glucuronidase) or useful for treating (for example, bFGF, bcl-2, CNTF or PAI) an ocular disease, is an effective means of treating the disease. These examples show that the procedure is not limited by means of incorporation, tissue type or disease.

Thus, the proffered evidence demonstrates the applicability of the invention for the treatment of any genetic ocular disease or a non-genetically based ocular disease associated with a lysosomal storage disease. Specific vector constructs comprising transgenes to be utilized for a particular genetic ocular disease and dosages to be used were within the ordinary knowledge of one skilled in the art. Further, the evidence demonstrates that a therapeutically effective amount of protein can be achieved by the claimed method. The evidence also demonstrates the effectiveness of the claimed invention in postmitotic cells, *e.g.* photoreceptors. Lastly, the evidence demonstrates the effectiveness of the invention in genetic ocular diseases caused by dominant mutated genes (see Exhibit H, demonstrating the effectiveness of the claimed

invention in a mouse model, *rds*, for autosomal dominant retinitis pigmentosa).

Thus, Applicant submits that the specification fully enables one of skill in the art to make and use the invention without undue experimentation.

The Office Action discusses the factors enumerated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In that case, the claims were drawn to methods of immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. The claims were rejected by the Examiner, affirmed by the Board, as requiring undue experimentation in the creation of the monoclonal antibodies. The Federal Circuit reversed, on the basis that the experimentation required was not "undue". The steps for the creation of the monoclonal antibodies, as outlined in by the Federal Circuit, were provided:

a) an animal is immunized with the antigen of choice;
b) after a period of time, the spleen is removed;
c) the lymphocytes are separated from other spleen cells;
d) the lymphocytes are mixed with myeloma cells, and treated to fuse the cells; and
e) hybridoma cells that secrete the desired antibodies must be isolated from the "enormous mixture" of other cells, using a series of screening steps, including
    i) culturing the cells such that only hybridoma cells grow;
    ii) hybridomas are isolated and cloned, by placing single hybridoma cells in separate chambers and growing them;
    iii) the secreted antibodies from each clone are screened to see if they bind to the antigen, a step which frequently requires the screening of "hundreds" of clones.

In the instant application, the steps for treating an ocular disease are:

a) identify a protein associated with or useful for treating an ocular disease;
b) introduce the nucleic acid encoding the protein into a means for delivering it to an *in situ* ocular cell;
c) introduce the nucleic acid to the cell under conditions permissive for its uptake; and
d) determine the efficacy of the treatment.

In comparison with the *Wands* procedures, the treatment of ocular disease by the present methods is not "undue experimentation".

Based on the above arguments and amendments, Claims 13-22 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Therefore, Applicant respectfully requests that the Examiner withdraw this rejection.

Claim Rejections - 35 USC § 112, second paragraph

Claims 13-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses.

The Examiner states that Claim 13 and its dependent claims, and Claim 22, are incomplete, because the claimed methods lack a step or steps linking the steps of (a) incorporating exogenous nucleic acid into an in situ ocular cell, (b) the uptake of said exogenous nucleic acid, and (c) the expression of said exogenous nucleic acid, to the recited preamble "treating a genetic ocular disease".

Applicant submits that these Claims are definite. The Claimed invention is drawn to incorporating an exogenous nucleic acid encoding a protein associated with an ocular disease into an ocular cell, *in situ*, *i.e.* into the eye of an animal, whereby the exogenous nucleic acid is expressed. Thus, once to exogenous nucleic acid is incorporated into an ocular cell, and expressed, the resulting protein effectively treats the ocular disease. This step links the method to treating a genetic ocular disease.

The Examiner requests clarification as to the term "treating", as applied in Claims 13, 22 and the dependent claims. By treating, it is meant, as shown in

the Claims, introducing an exogenous nucleic acid encoding a protein associated with an ocular disease into a cell having that disease. "Treatment" is defined in the specification, on page 15, lines 6-8, as "alleviat[ing] the symptoms." In addition, the term is well known in the art and one skilled in the art would understand that treating a disease is intended to produce a useful result, alleviating the effect of a disease. This would include curing, stabilizing and slowing the decline of a genetic ocular disease. The metes and bounds of the claim relate to an exogenous nucleic acid encoding a protein associated with an ocular disease.

The Examiner requests clarification as to the phrase "said lysosomal storage disease", as applied in Claim 22. The specification, at page 10, lines 18-31, defines ocular disease to include numerous conditions, including lysosomal storage disease, that cause ocular disorders or disfunctions. The Examiner is also referred to Exhibit C, which discusses a lysosomal storage disease in the eye.

For the foregoing reasons, Applicant respectfully requests withdrawal of the rejection.

Double Patenting

Claims 13-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (6, 9-12 and 15-19) of copending Application No. 09/018599.

Applicant wishes to defer addressing this rejection until claims are allowed.

Conclusion

Applicant submits that the claims are now in condition for allowance and an early notification of such is solicited.

Respectfully submitted,

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